

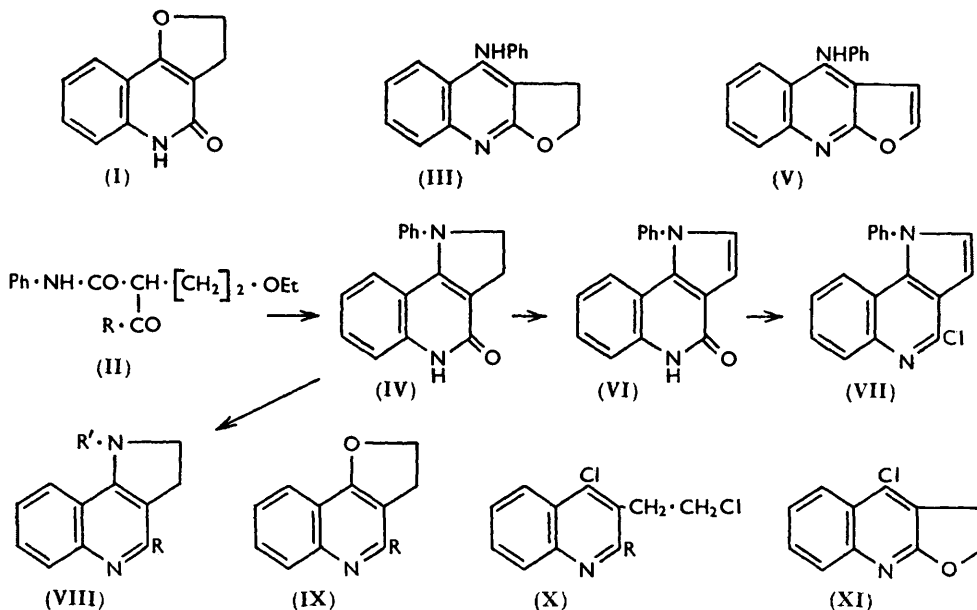
686. The Preparation of a Pyrrolo(3':2'-3:4)quinolone from (2-Ethoxyethyl)malondianilide.

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The structure of 1:2:4':5'-tetrahydro-2-oxo-1'-phenylpyrrolo(3':2'-3:4)quinoline (IV), prepared from (2-ethoxyethyl)malondianilide in refluxing diphenyl ether, was established by degradation to 4':5'-dihydro-1'-phenylpyrrolo(3':2'-3:4)quinoline (VIII; R = H, R' = Ph) which was synthesised.

THE intermediate in the preparation¹ of the dihydrofuranquinolone (I) from aniline and ethyl (2-ethoxyethyl)malonate in boiling diphenyl ether is probably the monoanilide (II; R = OEt). When the dianilide (II; R = NHPH) was heated in diphenyl ether, a new product, C₁₇H₁₄ON₂, was obtained in good yield.

The compound can be formulated as the dihydrofuranquinoline (III) or the pyrroloquinolone (IV), on the basis of its mode of formation and molecular formula. Dehydrogenation with palladium-charcoal gave the derivative, C₁₇H₁₂ON₂, (V) or (VI).



The intense infrared absorptions of the two new compounds at 1640—1650 cm^{-1} (NH·CO in a 2-quinolone²) favour the pyrroloquinolone structures (IV) and (VI), but the alternatives (III) and (V) are not excluded, as some anilino-derivatives absorb in the same infrared region.³

Reactions with phosphorus oxychloride confirmed the view that the compounds were quinolones. The dehydrogenation product gave the monochloroquinoline (VII), which showed no infrared absorption in the 1630—1700 cm^{-1} region. The compound, C₁₇H₁₄ON₂, afforded a dichloro-compound. This was not a derivative of the anilinoquinoline (III), formed by cleavage of the dihydrofuran ring, but a hydrochloride, from which the chloroquinoline (VIII; R = Cl, R' = Ph) was obtained with alkali.

The dehydrogenation product was unaffected by hydrobromic acid in boiling acetic

¹ Grundon, McCorkindale, and (in part) Rodger, *J.*, 1955, 4284.

² Grundon and McCorkindale, *J.*, 1957, 2177.

³ Bellamy, "The Infra-red Spectra of Complex Molecules," Methuen, London, 1956, p. 219.

acid, or by hydrochloric acid at 180°, in accord with the pyrroloquinolone structure (VI) : 4-anilinoquinolones are hydrolysed by acid to 4-quinolones.⁴ The compound, C₁₇H₁₄ON₂, on vigorous acid hydrolysis, gave the dihydrofuranquinolone (I).

The proof of structure was completed by catalytic reduction of the chloro-compound (VIII; R = Cl, R' = Ph) to 4' : 5'-dihydro-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (VIII; R = H, R' = Ph), which was synthesised.

Hörlein, Andersag, and Timmler⁵ have prepared recently a series of dihydropyrroloquinolines [for example, (VIII; R = R' = Me; and R = Me, R' = CH₂Ph)] by heating the chloroquinoline (X; R = Me) with phenol and the appropriate amine. The chlorodihydrofuran(3' : 2'-3 : 4)quinoline² (IX; R = Cl) furnished, with hydrogen and palladium-charcoal, the dihydrofuranquinoline (IX; R = H), which was converted by phosphorus oxychloride into the dichloro-derivative (X; R = H). This, when heated with aniline and phenol, yielded the dihydropyrrolo(3' : 2'-3 : 4)quinoline (VIII; R = H, R' = Ph) identical with that prepared from the quinolone (IV).

In an attempt to synthesise the anilinoquinoline (III), the linear chlorodihydrofuran(2' : 3'-2 : 3)quinoline² (XI) was heated with phenol and aniline. The pyrroloquinolone (IV) was the only product isolated.

EXPERIMENTAL

(2-Ethoxyethyl)malondianilide (II; R = NHPH).—Nitrogen was passed slowly through a mixture of ethyl (2-ethoxyethyl)malonate (50 g.) and aniline (40.1 g.) at 180–190° (bath). After ethanol (2 mols.) had been evolved (4 hr.), the mixture was allowed to cool and solidify. Trituration with light petroleum (b. p. 40–60°) and then with ethanol, gave the *dianilide* (52.4 g., 75%), m. p. 153–154°, separating from ethanol in needles, m. p. 161–162° (Found : C, 69.4; H, 6.5; N, 8.8; OEt, 13.5. C₁₉H₂₂O₃N₂ requires C, 69.9; H, 6.8; N, 8.6; IOEt, 13.8%).

1 : 2 : 4' : 5'-Tetrahydro-2-oxo-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (IV).—(2-Ethoxyethyl)malondianilide (11.3 g.) was heated in diphenyl ether (50 c.c.) under reflux, the by-products (ethanol and water) being allowed to escape. After 5 hr., light petroleum (b. p. 40–60°) was added, giving a solid. By crystallisation from pyridine, the *dihydropyrroloquinolone* was obtained as pale brown prisms (5.14 g., 59%), m. p. 238–240°, raised to 246–247° by repeated recrystallisation from pyridine [λ_{\max} . 232 (ϵ 41,700), 268 (shoulder) (ϵ 9100), 331 m μ (ϵ 13,200)], ν_{\max} . (in KBr) 1640(s) cm.⁻¹ (Found : C, 78.2; H, 5.6; N, 11.0. C₁₇H₁₄ON₂ requires C, 77.8; H, 5.4; N, 10.7%).

1 : 2-Dihydro-2-oxo-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (VI).—1 : 2 : 4' : 5'-Tetrahydro-2-oxo-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (0.5 g.) in diphenyl ether (15 c.c.) was heated under reflux with 10% palladium-charcoal (0.2 g.) for 15 hr., and the catalyst was removed by filtration. Addition of light petroleum precipitated the *pyrroloquinolone* (0.32 g., 64%), m. p. 249–250°, crystallising from ethanol in colourless prisms, m. p. 252–254°, λ_{\max} . 238 (ϵ 63,100), 274 (ϵ 7200) 284 (ϵ 6900), 315 (ϵ 9600), 328 m μ (ϵ 11,200), ν_{\max} . (in KBr) 1650(s) cm.⁻¹ (Found : C, 78.2; H, 4.4; N, 10.8. C₁₇H₁₂ON₂ requires C, 78.4; H, 4.6; N, 10.8%).

2-Chloro-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (VII).—The foregoing pyrroloquinolone (0.5 g.) and phosphorus oxychloride (5 c.c.) were refluxed for 1 hr., and the excess of reagent was then removed under reduced pressure. The solid, obtained by the addition of water, crystallised from ethanol giving the *chloropyrroloquinoline* as colourless prisms (0.45 g., 84%), m. p. 143–144°, unchanged by recrystallisation from ethanol (Found : C, 73.3; H, 3.9; N, 10.7; Cl, 12.7. C₁₇H₁₁N₂Cl requires C, 73.2; H, 4.0; N, 10.1; Cl, 12.7%).

2-Chloro-4' : 5'-dihydro-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (VIII; R = Cl, R' = Ph).—The dihydropyrroloquinolone (VI) (2 g.) and phosphorus oxychloride (13 c.c.) were refluxed for 1 hr., and the excess of reagent was removed. Addition of water gave the *hydrochloride* of the required base as a yellow solid (1.98 g., 81%), m. p. 180–186°, separating from ethanol in yellow prisms with unchanged m. p., ν_{\max} . (in KBr) 2421(s) cm.⁻¹ (\geq NH⁺) (Found : C, 64.6; H, 4.7; Cl, 22.7. C₁₇H₁₄N₂Cl₂ requires C, 64.4; H, 4.5; Cl, 22.4%).

A solution of the hydrochloride in chloroform was shaken with 0.5N-aqueous sodium hydroxide, dried, and evaporated, giving the *chloroquinoline*, m. p. 146–148°, quantitatively.

⁴ von Braun and Heymons, *Ber.*, 1930, **63**, 3191; Backeberg, *J.*, 1931, 2814.

⁵ Hörlein, Andersag, and Timmler, U.S.P. 2,691,023/1954 (*Chem. Abs.*, 1955, **49**, 14,813).

The analytical sample crystallised from ethanol in colourless needles, m. p. 149—150°, v_{\max} . (in KCl) 1613(w), 1598(m), 1567(s), 1502(s) (Found : C, 73.0; H, 4.6; N, 10.6; Cl, 12.2. $C_{17}H_{13}N_2Cl$ requires C, 72.7; H, 4.7; N, 10.0; Cl, 12.6%).

Hydrolysis of 1 : 2 : 4' : 5'-Tetrahydro-2-oxo-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline.—The quinolone (1 g.) and hydrochloric acid (10 c.c.) were heated in a sealed tube at 150—160° for 1 hr., and the solution was diluted with water and extracted with chloroform. Concentration of the chloroform solution to small bulk gave a yellow solid (0.15 g.), m. p. 265—275°, crystallising from ethanol in pale yellow prisms, m. p. 276—278°, shown to be identical with 1 : 2 : 4' : 5'-tetrahydro-2-oxofurano(3' : 2'-3 : 4)quinoline¹ by a mixed m. p. determination and by infrared spectra.

4' : 5'-Dihydrofurano(3' : 2'-3 : 4)quinoline (IX; R = H).—A solution of 2-chloro-4' : 5'-dihydrofurano(3' : 2'-3 : 4)quinoline² (2 g.) in ethanol (150 c.c.) containing potassium hydroxide (1.5 g.) was hydrogenated (1 mol. in 2½ hr.) at atmospheric pressure and room temperature with 10% palladium-charcoal (1 g.). The catalyst was removed, the solution evaporated, and the residue extracted with chloroform. The chloroform solution was shaken with several portions of aqueous acetic acid, and the combined acid solutions were made alkaline with aqueous sodium hydroxide and extracted with chloroform. Evaporation of the chloroform afforded the *dihydrofuranoquinoline* as a yellow solid (1.65 g., 99%) separating from light petroleum (b. p. 40—60°) in colourless plates, m. p. 95—96° (Found : C, 77.1; H, 5.0; N, 8.0. $C_{11}H_9ON$ requires C, 77.2; H, 5.3; N, 8.2%).

4-Chloro-3-2'-chloroethylquinoline (X; R = H).—4' : 5'-Dihydrofurano(3' : 2'-3 : 4)quinoline (0.5 g.) and phosphorus oxychloride (5 c.c.) were refluxed for 2 hr., excess of oxychloride was removed under reduced pressure, and water was added. Chloroform extraction afforded the *chloroquinoline* (0.26 g., 40%), crystallising from light petroleum (b. p. 40—60°) in colourless rods, m. p. 75—76° (Found : C, 58.4; H, 3.9; N, 5.9. $C_{11}H_9NCl_2$ requires C, 58.4; H, 4.0; N, 6.2%).

After the above product had been removed, the aqueous solution was made alkaline with sodium hydroxide. Chloroform extraction gave a colourless solid (0.11 g.), m. p. 94—96°, alone or mixed with the starting material.

4' : 5'-Dihydro-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (VIII; R = H, R' = Ph).—(a) 2-Chloro-4' : 5'-dihydro-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline (0.157 g.), ethanol (15 c.c.), and 10% palladium-charcoal (0.1 g.) were hydrogenated at room temperature and atmospheric pressure until 1 mol. of hydrogen had been absorbed. The catalyst was removed and the solution evaporated. The residue in benzene-chloroform (1 : 1) was chromatographed on alumina. Elution with the same solvent, evaporation, and crystallisation from light petroleum (b. p. 60—80°) gave the *dihydropyrroloquinoline* in colourless needles (0.074 g., 54%), m. p. 109—112° (Found : C, 82.9; H, 5.8; N, 11.2. $C_{11}H_{14}N_2$ requires C, 82.9; H, 5.7; N, 11.4%).

(b) A mixture of 4-chloro-3-2'-chloroethylquinoline (0.13 g.), phenol (0.12 g.), and aniline (0.22 g.) was heated at 170—180° (bath) for 3 hr., treated with 2N-aqueous sodium hydroxide, and extracted with chloroform. Evaporation of the chloroform solution furnished a dark-brown oil which was heated at 110° (bath)/0.1 mm. for 1 hr. to remove excess of aniline. A sublimate was obtained as a white solid (0.01 g.), m. p. 71—76°, undepressed by mixing with the starting material.

The residue was extracted with ether, and the ether solution was evaporated, giving a colourless solid (0.092 g.), m. p. 84—89°. Crystallisation from light petroleum (b. p. 40—60°) afforded the *dihydropyrroloquinoline* (0.076 g., 54%), m. p. 112—113°, undepressed by admixture with a sample prepared as in (a). The infrared spectra of the two samples were identical.

Reaction of 4-Chloro-4' : 5'-dihydrofurano(2' : 3'-2 : 3)quinoline with Aniline.—A mixture of the chlorofuranoquinoline² (1 g.), phenol (1 g.), and aniline (2 g.) was heated at 170—180° (bath) for 3 hr., and treated with 2N-aqueous sodium hydroxide. The precipitate was collected, and, after being washed with aqueous acetic acid and water, was obtained as a colourless solid (0.97 g.), m. p. 182—190°. Crystallisation from pyridine gave 1 : 2 : 4' : 5'-tetrahydro-2-oxo-1'-phenylpyrrolo(3' : 2'-3 : 4)quinoline as colourless prisms (0.615 g., 50%), m. p. 246—248°, not depressed on admixture with authentic material. The infrared spectra of the two samples were identical.

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